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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,738	VALLERA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,12,15,17-25,34 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,15,17-25,34 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 11/6/03 have been entered. Claims 1, 34, 36, and 38 have been amended. Claims 1-9, 11, 12, 15, 17-25, 34, and 36-43 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 11/6/03 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 stands rejected, and the rejection has been modified under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a subject with a tumor expressing a second member of an affinity pair wherein the affinity pair is an IL-4 receptor, wherein the method comprises intravenous administration of recited targeting T lymphocytes expressing a first member of the affinity pair, does not reasonably provide enablement for treating said tumors by any route of administration of said targeting T lymphocytes expressing any affinity pair. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to the type of tumor cells encompassed by the claim, since claim 34 has been amended to recite that cancer cells expressing the second member of the affinity pair on its surface, and example 6 of the specification has shown that intravenous administration of CTL cells transfected with the first member of the affinity pair has postponed the tumor growth, this portion of the previous rejection is withdrawn.

However, applicants fail to address the issue with respect to the route of administration, therefore, the rejection stands. The specification fails to teach whether cytotoxic T lymphocytes could be administered by means other than intravenous injection, for example when they are administered from a remove site far from circulation, whether the cells could enter the circulation in a sufficient amount to reach the site of the target and treating the cancer effectively. Accordingly, the disclosure fails to support the full scope of the claimed invention.

The amended claim 34 recites, "Wherein the subject comprises the cancer cell for which the targeting cell is specific and on the surface of which the second member of the affinity pair is expressed". Accordingly, the practice of the invention requires identification of an affinity pair that is specifically expressed in the cancer cell, and only so the targeting T cells transduced with the first member of the affinity pair could be used to specifically target the tumor cell. Claims 3-9 identified numerous cytokines, adhesion molecules, signal transduction receptors, hormones, and death domain family molecules as the affinity pairs.

However, it is common knowledge that these molecules are not specific for cancer or tumor cells, they are distributed in variety of cells, particularly immune system cells. Upon intravenous injection, the claimed targeting cells would not only target the tumor cells that may express the receptors for the cytokines, but also by-stander cells in the circulation. Therefore, except for IL-4 and IL-3 (known to be used for targeting tumor cells as taught by *Chan and Debinski*), the specification fails to teach which of the molecules are particularly abundant on the tumor cell surface. Further, the specification teaches, "*the targeting cell preferably should not express a high level of receptors that bind targeting domain of the fusion protein. More preferably, the targeting cells should express no such receptors*" (Specification, page 12, lines 22-25). However, receptors for the recited cytokines such as IL-1 and IL-2, and death domain molecules such as CD95 are present on T lymphocytes, high levels on activated T cells (the designated targeting cells). Ligand for a cell adhesion receptor such as ICAM-1 is present in all leukocytes including T lymphocytes. Accordingly, the claims and the specification are contradictory. Interestingly, it is noted that affinity pair that may be specific for tumor is the antigen and antibody affinity pair, however, the claims require that the targeting cell expressing the antigen, not the antibody, the specification fails to teach and it is unclear how an antigen that may be expressed in a tumor cell can be used to target the tumor cell, which antibody would expressed in a tumor cell of a host? In view of the above considerations, it appears that the specification fails to provide an enabling disclosure to support the full scope of the claims.

Accordingly, for reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-38 stand rejected and Claims 1-9, 11, 12, 15, 17-25, 34, and 36-43 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the previous action, it was indicated

> Claim 36 recites the limitation, "said cell population of claim 22" in line 1, and the limitation, "said cells" in line 4, 5, and 10. There is insufficient antecedent basis for this limitation in the claim.

Applicants fail to respond to the first issue, and amended claim 36 to recite "comprising cells" as an attempt to address the second issue. The new claim recitation is vague and indefinite because it is unclear what cells the claim refers to, thus the metes and bounds of the claims are unclear. Amending the phrase, "said cell population" and "said cells of said preparation" to "said cells of said population" would obviate this rejection.

Claims 1-9, 11, 12, 15, 17-25, 34, and 36-43 are vague and indefinite because of the claim recitation, "significant binding affinity". The specification does not provide a standard for ascertaining the requisite degree of the "significant" binding affinity, and one of the skill in the art would not be reasonably

apprised of the scope of the invention. Amending the claim to recite "specific binding affinity" may obviate this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), in view of *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80).

Applicants argue that '387 patent fails to mention a cytokine-toxin construct, nor T cells with significant binding affinity for a cancer cell, that there is not the least suggestion in the '387 patent that (a) coding sequences in retroviral vectors transduced into TIL encode a cytokine alone or a toxin alone, let alone a fusion protein containing both; or (b) that TIL be used for the delivery of anything,

let alone such a fusion protein. Applicants also argue that the reference to TIL occurs in the context of use of retroviruses in general and in tracking the migration of the TIL after injection into cancer patients, there is no teaching or remotest suggestion that the TIL are transduced with anything other than a detectable marker.

The argument has been fully considered but found not persuasive. This is because applicant's arguments attack the references individually, applicants are reminded one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the '387 patent is relied upon as a showing that the ordinary skilled artisan knows constructing a targeting vector comprising a cytokine targeting domain and using such for transfecting T lymphocytes. The *Chan et al and Debinski et al* are relied upon as a showing that the ordinary skilled artisan knows to target the cancer killing drug with the cytokine receptors expressed on the surface of cancer cells such as leukemia cells, and how to construct an immunotoxin fusion protein. The *Chen* reference is relied upon as a showing that the ordinary skilled artisan knows to use transduced T lymphocytes as immunotoxin carrier.

'387 patent clearly teach a retroviral vector for targeted gene delivery to a specific cell population (see particularly the title and the abstract) and such is achieved by including a chimeric fusion protein-coding region in the vector, wherein the targeting domain of the fusion protein is a cytokine (the first member

of an affinity pair) such as IL-2 (column 6, line 1). The claims do not have the limitation that the cytokine was encoded alone, so as long as the vector comprises a nucleic acid sequence encoding a non-antibody protein having a targeting function, it meets claim limitation. '387 patent also teaches that the vector could be used for various purposes such as delivering a gene to a target cell, introducing a marker into the target cell, enhancing the expression of a gene or inserting an otherwise therapeutic gene to modulate the growth or differentiation of the target cell or including a toxin domain to bring about the quiescence or death of the target cell (the paragraph bridging columns 25-26). In addition to discussing tagging TIL, the '387 patent teaches, "SPECIFIC TRASDUCTION OF T CELLS WILL ALSO ALLOW MANIPULATION OF IMMUNE DISORDERS IN VIVO, BY TARGETING T CELLS TO EITHER ENHANCE T CELL PROLIFERATION OR TO SUPPRESS T CELL PROLFERATION USING, FOR EXAMPLE, NEGATIVE GROWTH REGULATORS, TOXINS OR SUICIDE GENES"(column 26, lines 50-56, emphasis added). Thus, '387 patent suggested genetically modifying T lymphocyte and including a cytokine targeting domain. With regard to the tumor affinity of the T cells, it is well known in the art that the cytotoxic T cells specific for cancer would have such affinity. To this end, the '387 patent teaches, "THIS (transfected T lymphocyte or its precursor) HAS IMPLICATIONS FOR THE TREATMENT OF CANCER" (column 26, line 45). Thus, '387 patent suggested genetically modifying T lymphocyte for tumor therapy, and a tumor specific T lymphocyte would have specific binding affinity to the specific tumor cells.

With respect to the cytokine-toxin fusion construct, although the '387 patent does not clearly teach such, the construct was taught by *Chan et al,* and

Debinski et al. Applicants argue that *Chan et al, Debinski et al, and Chen et al* make no mention of any isolated mammalian cells transduced with such vectors, let alone a T cell with significant binding affinity for a cancer cell.

Here again, the rejection is based on combinations of references. In addition to the '387 patent, *Chen et al* clearly teach genetically modifying T lymphocytes with a targeted toxin, and using the genetically modified T lymphocytes as a carrier for the targeted toxin (e.g. 1st paragraph, page 78). Although *Chen et al* do not use a cytokine as the targeting domain, such has been taught by '387 patent, *Chan et al*, and *Debinski et al*. The *Chan et al and Debinski et al* are relied upon as a showing that the skilled artisan knows to target the cancer killing drug with the cytokine receptors expressed on the surface of cancer cells such as leukemia cells, and how to construct an immunotoxin fusion protein. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, since the knowledge of constructing an immunotoxin is generally available in the art, using lymphocytes delivering a genetic construct having tumor-killing toxin is also available in the art, there is

sufficient motivation to employ the immunotoxin construct in the method of '387 patent and *Chen* reference.

With respect to claims 38-42 drawn to the cytokine-toxin construct in a *viral* vector, it appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burke, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. As discussed in the immediate preceding paragraph, there is sufficient practice using a viral vector carrying a genetic construct, since they are more efficient in cellular transfection. Thus, the state of the art suggests that it would have been obvious to use a viral vector for carrying the construct encoding immunotoxin.

Apparently, at least two different utilities are proposed for obtaining a T lymphocytes comprising the cytokine-toxin genetic construct, i.e. for targeting the unwanted T lymphocytes in immune regulation, and for carrying a toxin to tumor cells in tumor immune therapy for added strength of tumor killing. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al, Chan et al,* and *Chen et al*, by making a retroviral vector containing a genetic construct comprising a targeting domain and a toxin domain and using such for transducing tumor specific T lymphocytes with a reasonable expectation of

success. The ordinary skilled artisan would have been motivated to modify the prior art teachings to arrive at the claimed invention because the utilities of the modified T cells had been clearly taught by the skilled artisan, i.e. to destroy unwanted T cells, and to enhance the tumor-killing effect of the tumor-specific CTL. The instant situation is also amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of tumor specific CTLs, and immunotoxins- all taught to be useful for the treatment of cancer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 3 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80), as applied to claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-

42 above, and further in view of *Cochlovius et al* (Cancer Immunol Immunother 1998;46:61-6).

In the response, in addition to attacking the references relied upon individually, Applicants argue that the combination of Cochlovius et al and the '387 patent lacks disclosure of transduction of any cell, let alone one with significant binding affinity for a cancer cell. Applicants particularly argue that Cochlovius et al discloses transduction with vector expressing a cell adhesion receptor, not a ligand for a cell adhesion receptor as specified by claim 3, and the homing receptor serves merely to improve the homing capacity to skin of CTL not producing any exogenous cytotoxic molecule.

In response, the invention as a whole was taught by the combined teachings of the references as discussed above. *Cochlovius et al* teach genetically modifying melanoma-specific CTLs with the CD44v10 as the targeting domain to target the CTLs to the skin for killing locally (skin) growing melanoma and skin metastases (§ introduction). With respect to the cell adhesion molecules, Mesh database defines the term "Adhesion molecules" as "SURFACE LIGANDS, USUALLY GLYCORPROTEINS, THAT MEDIATE CELL-TO-CELL ADHESION" (emphasis added), here the adhesion molecule and its ligand are relative to each other, there is no clear restriction with regard to the ligand or the molecule itself, as indicated in the previous Office action, CD44 is a glycoprotein, a ligand for haluronic acid on skin cell surface, the basis for targeting the CTL to the skin. Moreover, even if CD44 were considered as a receptor, not the ligand, it would have been obvious for the ordinary skilled in the art to use the concept of the

receptor-ligand pair that mediating cell-to-cell adhesion, to use either the ligand or the receptor as the first member of the affinity pair.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al,* and *Chen et al*, with that of *Cochlovius et al* by selecting a ligand that best suits their need in making the genetic construct with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention as done by *Cochlovius et al* for targeting T cells to the skin. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80) as applied to claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42 above, and further in view of *Clay et al* (Pathol Oncol Res 1999 Jan;5:3-15) or *Buchsbaum et al* (US 6,001,329).

Applicants argue that neither *Clay et al, nor Buchsbaum et al* teach or suggest a viral vector encoding the immunotoxin molecule, or use of non-antibody targeting domains in immunotoxins.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the invention as a whole was taught by the combined teachings. Here, *Clay et al, or Buchsbaum et al* teachings are relied upon for using viral vectors transducing lymphocytes or other mammalian cells for gene delivery. In addition to teaching radiolabled immunotoxin proteins, *Buchsbaum et al* also teach using adenoviral vectors delivering desired genes to tumor cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al,* and *Chen et al*, with that of *Clay et al* and *Buchsbaum et al* by selecting a viral vector that best suits their need in making the genetic construct with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention as suggested by *Clay et al.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. In response to applicant's argument that there is no suggestion to combine the references, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
January 23, 2004